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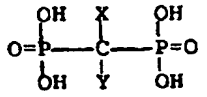
(54) Title: THE USE OF BISPHOSPHONATES IN BONE SURGERY



(I)

(57) Abstract

The invention relates to the use of a compound of formula (I), wherein X is H, OH, Cl, F or a methyl group and Y is Cl, OH, $-(CH_2)_2-N(CH_3)-(CH_2)_4-CH_3$, $-(CH_2)_n-CH_3$ or $-(CH_2)_n-NH_2$, where n is zero or an integer of 1 to 8, -NHZ, where Z is pyridinyl or cycloheptyl, -SZ', where Z' is pyridinyl or chloro-substituted phenyl, or Y is a pyridinylsubstituted lower alkyl chain; or a non-toxic, pharmaceutically acceptable salt or ester thereof for the manufacture of a pharmaceutical composition to be used in enhancing the formation of bone tissue and/or eliminating late complications subsequent to bone surgery in a bone surgery patient before and/or after said surgery.

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THE USE OF BISPHOSPHONATES IN BONE SURGERY

This invention relates to the use of a certain group of bisphosphonates for the regeneration of bone tissue and/or elimination of late complications subsequent to bone surgery. More particularly, the invention concerns the use of clodronate to enhance bone tissue formation after surgical replacement of endo-osteal material such as implantations, particularly dental implantations, and transplantations.

Bisphosphonates are synthetic organic compounds structurally related to pyrophosphate in that the pyrophosphate P-O-P-bond is replaced by a P-C-P-bond. In contrast to pyrophosphate, bisphosphonates are resistent to enzymatic hydrolysis in osseous tissue. The bisphosphonates are potent inhibitors of bone resorption and they have been successfully used in the treatment of hypercalcemia caused by various reasons. A great number of bisphosphonates have been studied, but only clodronate, etidronate and pamidronate have reached wider clinical use.

The main effect of the bisphosphonates is their ability to inhibit bone resorption, but contrary to the effect on mineralization, the mechanism involved is cellular (Fleisch H, Drugs 1991; 42: 919-44). These different effects vary greatly according to the structure of the individual bisphosphonate compound. The half-life of circulating bisphosphonates is very short, in the order of minutes to hours. Of a given dose, 20 to 50 % is taken up by the skeleton, the rest being excreted in the urine. The half-life in bone is far longer and depends upon the turnover rate of the skeleton itself.

A review (Mian M et al., Int J Clin Pharmacol Res. 1991; 11: 107-14) of 126 publications on clinical studies concerning the use of clodronate in the therapy of bone

disease, involving 1930 patients, in order to evaluate the tolerability and the effects following short- and long-term administration of this drug, indicates that clodronate therapy does not have any clinically significant side-effects and confirm its tolerability and safety.

Of the many compounds belonging to the bisphosphonate family, clodronate has been widely used in hypercalcemia and osteolysis of malignancy (Bonjour J P and Rizzoli R, Calcif Tissue Int 1990; 46 Suppl: 20-25). All published reports indicate that clodronate can normalize plasma calcium in the majority of hypercalcemic, rehydrated cancer patients in whom increased bone resporption is the prevailing disturbed calcium flux (Fleisch H, Drugs 1991; 42: 919-44).

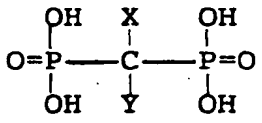
Various phosphonate compounds are also reported in the patent literature as being useful in the treatment of anomalous mobilization and deposition of calcium phosphate salts (bone mineral) in mammals. Reference is made to US patents 3,678,164; 3,662,066; 3,553,314; 3,553,315; 3,584,124; 3,584,125 and 3,641,246. US 3,683,080 discloses the use of clodronate and various other phosphonates for the treatment of anomalous calcification involving soft tissues and arthritic conditions. US 4,234,645 discloses clodronate as useful in the treatment of various collagen diseases.

As discussed above, bisphosphonates are well documented with respect to their ability to inhibit bone resorption in connection with various diseases. The use of these compounds to promote bone tissue formation subsequent to surgical operations relating to endo-osteal prosthesis such as hip prostheses, plates used in internal rigid fixation and various kinds of implantations; osteomyelitis after decorticalization of necrotics from the mandible or bone transplantations has, however, never been suggested. Particularly in dental implantation surgery, patients with

severe atrophy of the mandibular alveolar process are difficult to treat by conv ntional implant techniques. At the abutment connection operation mobile fixtures are found frequently. About half of the number of recorded failures occurred under the healing period (Adell R et al., Int J Oral & Maxillofac Surg 1990, 5: 347-359). Autogenous bone grafts used for severely resorbed ridge augmentation usually resorb to a considerable extent (Baker R D et al., J Oral Surg 1970; 37: 486-89).

It has now been found that bisphosphonates are useful to promote bone formation subsequent to bone surgery and to eliminate late complications due to implantations, particularly hip prostheses. For the purpose of this invention the term "bone surgery" shall be understood to include surgical operations relating to endo-osteal prostheses such as hip prostheses, plates used in internal rigid fixation and various kinds of implantations of artificial implants into the human body such as dental implants; treatment of osteomyelitis after decorticalization of necrotics from the mandible; and bone transplantations. The invention particularly concerns oral surgery, especially the introduction of artificial tooth implants.

The present invention relates to the use of a compound of formula (I)

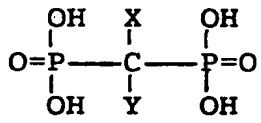


(I)

wherein X is H, OH, Cl, F or a methyl group and Y is Cl, OH, $-(CH_2)_2-N(CH_3)-(CH_2)_4-CH_3$, $-(CH_2)_n-CH_3$ or $-(CH_2)_n-NH_2$, where n is zero or an integer of 1 to 8, -NHZ, where Z is pyridinyl or cycloheptyl, -SZ', where Z' is pyridinyl or chloro-substituted phenyl, or Y is a pyridinylsubstituted lower alkyl chain; or a non-toxic, pharmaceutically

acceptable salt or ester thereof for the manufacture of a pharmaceutical composition to be used in enhancing the formation of bone tissue and/or eliminating late complications subsequent to bone surgery in a bone surgery patient before and/or after said surgery.

The present invention relates further to a method of enhancing the formation of bone tissue and/or eliminating late complications subsequent to bone surgery comprising administering an amount, which is safe and sufficient to promote the formation of bone tissue and/or eliminate late complications, of a compound of formula (I)



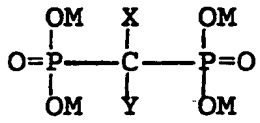
(I)

wherein X is H, OH, Cl, F or a methyl group and Y is Cl, OH, $-(CH_2)_2-N(CH_3)-(CH_2)_4-CH_3$, $-(CH_2)_n-CH_3$ or $-(CH_2)_n-NH_2$, where n is zero or an integer of 1 to 8, -NHZ, where Z is pyridinyl or cycloheptyl, -SZ', where Z' is pyridinyl or chloro-substituted phenyl, or Y is a pyridinylsubstituted lower alkyl chain; or a non-toxic, pharmaceutically acceptable salt or ester thereof to a bone surgery patient before and/or after said surgery.

Particularly valuable members of formula (I) for the purpose of this invention are clodronate, where X and Y both are Cl; pamidronate, where X is OH and Y is $-(CH_2)_2-NH_2$; alendronic acid, where X is OH and Y is $-(CH_2)_3-NH_2$; neridronic acid, where X is OH and Y is $-(CH_2)_5-NH_2$; risedronic acid, where X is OH and Y is 3-pyridinylmethyl; tiludronate, where X is H and Y is 4-chlorophenylthio; YM-175, where X is H and Y is cycloheptylamino; BM-210995, where X is OH and Y is $-(CH_2)_2-N(CH_3)-(CH_2)_4-CH_3$ and etidronate, where X is methyl and Y is OH. The most preferable compound for the purpose of the invention is clodronate or its pharmaceutically

acceptable salts or esters.

The pharmaceutically acceptable salts and esters useful in the practice of this invention can be described by formula (II)



(II)

wherein X and Y are as defined above and M is hydrogen, a pharmaceutically acceptable cation, preferably an alkali metal cation such as sodium or potassium, or an alkyl or aryl moiety, e.g. an alkyl of 1 to 4 carbon atoms or phenyl.

For the purpose of the invention the compounds of formula (I) or their pharmaceutically acceptable salts and esters can be administered by various routes. The suitable administration forms includes systemic use such as oral formulations; parenteral injections including intravenous, intramuscular, intradermal and subcutanous injections; and suppositories. The compounds can also be administered locally by laying on or spreading the compounds or compositions thereof directly on the tissue to be treated.

The required dosage of the compounds of formula (I) or their salts will vary with the particular condition being treated, the severity of the condition, the duration of the treatment, the administration route and the specific bisphosphonate being employed. A single daily dose can range from 0.01 to 100 mg per kilogram body weight. Doses higher than 100/kg/day may produce toxic symptoms and should be avoided. For parenteral administration (s.c; i.p.; i.m.), the preferable bisphosphonate daily doses range from 0.5 to 20 mg/kg. For i.v. administration the most preferable daily doses are 0.5 to 5 mg/kg. For oral administration the preferred daily doses range from 10 to

100 mg/kg. For local treatment a solution of 5 to 100 mg/ml of a biphosphonate should preferably be used before replacement of endo-osteal material.

The medication should preferably start 1 to 3 weeks before the surgery to obtain the optimal bisphosphonate concentration in bone. After the surgery, the medication should preferably be continued for a period of 1 to 6 months.

The inventive idea was verified by animal and clinical tests. According to two separate studies with clodronate disodium, the methods and results of which are presented in detail below, the effect of clodronate on bone tissue formation is demonstrated.

In the first test, the effect of clodronate on bone regeneration was tested in rabbit tibia. An experimental model involving free bone transplantation to the tibia was developed. The tests revealed that clodronate had a positive effect on bone regeneration in the donor cavity and in the free bone grafts transplanted using a titanium screw. Clodronate-treated tibiae were more quickly and more extensively vascularized than the control tibiae.

The results of human studies, where the patients had an extra implant that was removed after a certain period of time, demonstrated that clodronate-medicated patients exhibited a more rapid bone formation than the unmedicated control group.

Because of the close structural and pharmacological relationship between clodronate and its analogues as represented by formula (I) above it is justified to believe that the remaining members of formula (I) also are effective to promote the bone tissue formation and to eliminate late complications after surgery.

EXPERIMENTS

I. Effect of clodronate on bone regeneration in rabbits

The aim of the study was to determine whether clodronate had a positive effect on vascularization and bone formation in the tibia of a rabbit in which bone was transplanted with the aid of a titanium screw.

Materials and methods

Sixteen skeletally mature (3.5 - 3.9 kg) New Zealand white male rabbits were used. The animals were divided into two groups. Each group consisted of eight animals (16 tibiae). One group received clodronate disodium (Bonefos^{R}, Leiras Oy, Finland) 25 mg/kg i.m. twice a week. The other group (control) was untreated.

The rabbits were anaesthetized with an i.m. injection of 2.8 mg of Ketalar^{R} (Parke-Davis, Spain) and 2.0 ml of Rompun^{R} (Bayer, Germany).

The proximal ends of both tibiae were exposed and the periosteum removed from the operative area. A piece of cortical bone 4 mm across was removed using a trepan bur. A 0.6 mm titanium implant screw (Filpin, Filpol Dental, Ireland) was screwed through the piece. The piece, perforated with the implant, was screwed into place 3 mm above the donor cavity. Reference is made to Figure 1 representing the rabbit tibia, where A means the implant, T the transplant and F the donor cavity. The upper drawing of the Figure represents the cross section and the lower drawing the tibia as seen from above.

The animals were divided into two groups: microangiography was performed on eight animals and histological staining specimens was carried out from the other eight animals. Roentgenological examinations with two steel wires with

knots twisted around the tibiae to determine the exact positions of implant and donor cavity wer performed. Reference is made to Figure 2, which discloses a lateral roentgen picture of tibia in the operation area. The letters A, T and F have the same meaning as in Figure 1.

Histological evaluation

Eight animals were killed for histological evaluations at various times after implantation: after 14 days (2 rabbits), 21 days (4 rabbits) and 35 days (2 rabbits). The number of control and clodronate-treated animals was the same each time.

Tibiae were fixed with 5 % phosphate-buffered formalin and toluine blue staining and hematoxylin eosin (HE) were carried out. Specimens were inspected under a light microscope and adverse effects or signs of inflammation were recorded.

Microangiography

Eight animals (4 controls, 4 treated) were killed after 21 days by means of an i.v. dose of pentobarbital.

Before death the abdominal artery and vein were exposed and an 18-gauge angiocath was inserted and tied in place. A 20 ml syringe containing heparinized saline was used to infuse the abdominal artery. Infusion continued until a clear venous effluent emerged from the transacted abdominal veins. A 100 ml syringe filled with an orange-colored silicone rubber compound (Micro-Fil^{R}, Canton Biomedical, Boulder CO, USA) was then injected until orange effluent emerged from the abdominal veins. After the compound had set for 4 hours, the tibiae were separated. The specimens were then sequentially dehydrated according to the cleaning technique of the manufacturer.

Using a scalpel, cross-sections were cut through the mid-portions of the grafts for vi wing and slide photography under a dissecting microscope. The absolute number of vessels penetrating the transplant host junction was counted by means of color transparencies (Eppley B et al., J Oral Maxillofac Surg 1988; 46: 391-98).

The vessel count was performed in the specimen where the most vessels were observed. Vessels were counted on two separate occasions by the same observers and the results were averaged. If the variation between two values was greater than 10 %, a third count was undertaken and the three counts were averaged. Vessel counts in both groups were compared using a paired t-test; P values less than 0.05 were considered significant.

Results

The clinical observations revealed that all wounds healed uneventfully.

Evaluation of angiogenesis

When counting the vessels, most of them were clearly visible. It was, however, difficult to count the small vessels in the bone-transplant and bone-donor cavity junctions. Because of the variation in the two values by the same observer the third count was undertaken in five specimens.

Donor cavities

The number of vessels penetrating into the donor cavities was greater in rabbits treated with clodronate than for the control. The results are given in Table I below and the difference is statistically significant ($P < 0.05$).

Table I

Number (x) of vessels penetrating donor cavity

	x	S.D.	Number of tibiae
Control	12.3	4.6	8
Clodronate treated	26.3	4.0	8

The difference in the amount of vessels can also be observed from the photographs of Figures 3 and 4. Figure 3 discloses a 21-day specimen from a rabbit treated with clodronate. Implant and transplant are located in the centre of the picture. The donor cavity is seen to the right of the transplant. It can be seen that many vessels penetrate the donor cavity and transplant. Figure 4 shows a 21-day specimen from an untreated rabbit. Only a small number of vessels penetrated the transplant.

Transplants

The transplants in the tibiae from the clodronate-treated animals became vascularized sooner and more extensively than in the tibiae from the control. The difference was statistically significant ($P < 0.05$). The results are presented in Table II.

Table II

Number (x) of vessels penetrating transplant

	x	S.D.	Number of tibiae
Control	4.75	1.7	8
Clodronate treated	13.0	4.0	8

The vessels penetrated closer to the centre of the cavity in the medicated rabbits than in the control group. In the medicated rabbits the number of vessels from one side of the specimens was greater than from the opposite side.

Histological findings

No signs of adverse tissue reactions or inflammation were observed when the specimen were studied under the light microscope.

Donor cavity

The 14-day control specimens exhibited slight collagen formation and were partly devoid of histologically visible elements in the middle part of the cavity. The clodronate-treated specimens exhibited more collagen formation than the control specimens. No empty spaces were seen. At three weeks, the control specimens exhibited only slight bone formation at the outer edges of the cavity. The inner part of the cavity was mainly filled with collagen and a sharp line between the cavity and bone was clearly seen. The clodronate-treated donor cavities were almost completely filled with new bone. Collagen was still found between new bone in the three-week specimens.

The five-week control cavities were partly filled with new bone, and the line between drilled cavity and bone was still seen in most parts of the cavity. The clodronate-treated cavities were completely filled with new bone and the drilling line was visible but the resolution between the donor cavity and old bone had started. Figure 5 illustrates a five-week control cavity. Bone regeneration is seen in middle of cavity and in drilling lines. The line between drilled cavity and bone is still seen in most parts of cavity. New bone formation with osteoblasts occurs occasionally in drilling line and also in centre of cavity. Figure 6 illustrates a five-week clodronate-treated

cavity. Cavity is completely filled with new bone and drilling line is still visible but there is a fusion between donor cavity and cortical bone. Figures 7 and 8 represent greater magnifications of Figure 6. In Figure 7 solid new bone and osteoblasts can be observed. Figure 8 shows that cortical and new bone are almost completely fused.

Transplants

The soft tissue and periosteum above the transplants contained more collagen in the clodronate-treated group than in the control animals at all stages. Fourteen-day control specimens exhibited necrotic bone with invading collagen. Treated transplants were beginning to be resorbed at their outer edges. Figure 9 represents a side-view of four-week clodronate-treated rabbit's tibia. New bone covers transplant. Periosteum is intact but thinner than that above non-operated area. Implant and transplant are in the middle of this specimen. Donor cavity is to the right from transplant and is the reason for new bone formation in normally empty rabbit's spongious bone.

Twenty-one-day transplants were partly resorbed. New bone in the resorbed areas was seen in the treated tibiae. No bone formation was seen in control transplants. Bone formation around the implant in the cortical bone area was solid in the clodronate-treated group. Figure 10 represents a clodronate-treated 21-day specimen. Transplant is partly resorbed and replaced with new bone. The letters A and T represent implant and transplant, respectively, as in Figure 1, and E represents new bone adjacent to transplant and cortical tibia.

In 35-day specimens there was new bone formation almost throughout the transplants in the treated tibiae. Only solid bone was seen in the control transplants.

Discussion

Regeneration of transplants occurs through microvascularization of the transplant. In a rat embryo study, Ray (Ray R D, Clin Orthop 1977; 87: 43-48) showed that vascularization of a rat embryo takes 3 to 4 weeks. In a review article, Burchardt (Burchardt H, Clin Orthop 1983; 174: 28-42) states that cancellous bone differs from cortical grafts as far as rates of revascularization are concerned. He suggested that revascularization of cancellous grafts can occur within hours as a result of end-to-end anastomoses from host vessels. Revascularization may be completed within two weeks (Ray R D; reference as above). A cortical graft is not penetrated by blood vessels until the sixth day (Ray R D; reference as above). Twenty-one days was selected on the basis of the results of a report by Eppley and co-workers (Eppley B et al., J Oral Maxifollfac Surg 1988; 46: 391-98) as bone regeneration time after implantation. They found that the vascularization of bone grafts in rabbits reached a maximum after 21 days.

The results of the present study confirm the results of earlier reports (Bonjour J P; Ray R D; both references given above) as far as the control group is concerned. In the medicated rabbits vascularization occurred more quickly than in the control group. The histological findings show clearly that clodronate-treatment makes better bone. The results of the study suggests that bisphosphonates, particularly clodronate, are useful in implant and bone transplant patients where there is a high risk of failure of bone regeneration.

II. Human tests

Material and methods

The material of this study were 20 edentulous patients.

They all came to the Institute of Dentistry, University of Turku, for an implantation procedure. The Institutional Review Board of the Faculty of Medicine at the University of Turku received the project in order to determine whether human subjects are placed at risk. The unanimous decision made by the Institutional Review Board was that the human subjects concerned in this activity would not be placed at any risk. Patients gave permission for an explantation of an extra implant. 10 patients got a daily dose of 1600 mg clodronate disodium until the extra implant was removed (the medicated group) and 10 patients got placebo. The medication and placebo administration, respectively, started one week before the surgery and continued for three weeks after the surgery.

Surgical technique

Routine method with five Astra implants was used. Fig. 11 is a front view human mandible with four Astra implants, where A means implants, E explanted implant with bone and N is the mandibular nerve. To avoid disturbances in neural function implants are usually placed between the ends of mandibular nerve. At the operation an extra 4 mm screw was installed in the midline of the mandible.

Bone remodelling

At a separate operation the 4 mm extra implant was removed with a trephan bore after 4 (10 patients, equally from both groups) and 12 weeks (10 patients, equally from both groups). The specimens were imbedded in acrylic blocks and divided in midline in two pieces. To the one piece a histological examination was performed. The other one was taken to a SEM-electromicroscopic examination. Electromicroscopic examination in bone-implant interspace and bone in three points with SEM/EDXA (energy dispersive X-ray analysis) was made. At the four different places, two in the upper cortical bone, one in the middle of the

implant and one in the bottom of that the following values are calculated: sodium, calcium, phosphor, magnesium and titan. Calcium/phosphor and calcium/magnesium ratio were calculated in 12 points.

Results

Clinical treatment

All the wounds healed well. Two patients had problems with their lower denture under the healing period. They were treated by taking away a part denture. No side-effects were recorded. One patient had pain in his hip orthopedic prosthesis. Those disappeared after clodronate medication.

Histological examinations

One month-specimens

Because all the mandibles were considerably resorbed and the length of explanted implant was 4 mm biopsied bone was cortical in all specimens. The histological results are shown in Figures 12 and 13, which both disclose the bone-implant specimen marked with E in Figure 11. Fig. 13 represents a greater magnification of Fig. 12. No spongious bone was seen. Soft gingival tissue covering the implants was healthy.

Histological examination revealed no more new bone in medicated than control-mandibles. There were no signs of inflammation. The space between implant and bone was mainly filled with collagen. In same points the contact between bone and implant was close. This is natural, because screwed Astra implants were used.

SEM-results

Table III shows the SEM results in human mandibles 4 weeks

after implantation of an extra Astra implant.The 10 000 x SEM figure is the same as that in Figures 11 and 12. The exact points where mineral concentrations are measured are shown with small numbers in Figure 14. The mean values of those standard points are given in Table III.

Table III

	CaO	P_2O_5	CaO/P_2O_5	Mg	Na
control	56	30	1.8	1.2	8.2
medicated	72	40	1.8	0.9	2.8

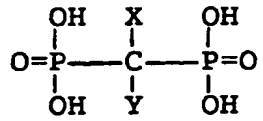
The values are given in weight percent.

Discussion

Histological and SEM-pictures were similar in both groups. No differences under light and SEM-cross-over pictures were seen. In one month specimens P_2O_5 and CaO are both significantly greater in the medicated than in control mandibles. This means that rapid bone formation had begun, osteoclasts have resorbed bone. Osteogenesis is more intensive in medicated than in control patients.

CLAIMS

1. The use of a compound of formula (I)



(I)

wherein X is H, OH, Cl, F or a methyl group and Y is Cl, OH, $-(CH_2)_2-N(CH_3)-(CH_2)_4-CH_3$, $-(CH_2)_n-CH_3$ or $-(CH_2)_n-NH_2$, where n is zero or an integer of 1 to 8, -NHZ, where Z is pyridinyl or cycloheptyl, -SZ', where Z' is pyridinyl or chloro-substituted phenyl, or Y is a pyridinylsubstituted lower alkyl chain; or a non-toxic, pharmaceutically acceptable salt or ester thereof for the manufacture of a pharmaceutical composition to be used in enhancing the formation of bone tissue and/or eliminating late complications subsequent to bone surgery in a bone surgery patient before and/or after said surgery.

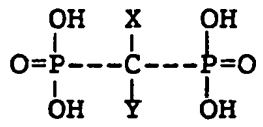
2. The use according to claim 1 wherein the compound is selected from the group consisting of clodronate, pamidronate, etidronate, alendronic acid, neridronic acid, risedronic acid, tiludronate, YM-175, BM-210995 and pharmaceutically acceptable salts and esters of said compounds.

3. The use according to claim 2 wherein the compound is clodronate or its pharmaceutically acceptable salt or ester.

4. The use according to claim 3 wherein the compound is clodronate disodium.

5. A method of enhancing the formation of bone tissue and/or eliminating late complications subsequent to bone surgery comprising administering an amount, which is safe and sufficient to promote the formation of bone tissue

and/or eliminate late complications, of a compound of formula (I)



(I)

wherein X is H, OH, Cl, F or a methyl group and Y is Cl, OH, $-(CH_2)_2-N(CH_3)-(CH_2)_4-CH_3$, $-(CH_2)_n-CH_3$ or $-(CH_2)_n-NH_2$, where n is zero or an integer of 1 to 8, -NHZ, where Z is pyridinyl or cycloheptyl, -SZ', where Z' is pyridinyl or chloro-substituted phenyl, or Y is a pyridinylsubstituted lower alkyl chain; or a non-toxic, pharmaceutically acceptable salt or ester thereof to a bone surgery patient before and/or after said surgery.

6. The method according to claim 5 which comprises administering an amount, which is safe and sufficient to promote the formation of bone tissue, of a compound of formula (I) or a non-toxic, pharmaceutically acceptable salt or ester thereof to a transplantation surgery patient.

7. The method according to claim 5 which comprises administering an amount, which is safe and sufficient to promote the formation of bone tissue, of a compound of formula (I) or a non-toxic, pharmaceutically acceptable salt or ester thereof to an endo-osteal prosthesis surgery patient.

8. The method according to claim 7 which comprises administering an amount, which is safe and sufficient to promote the formation of bone tissue, of a compound of formula (I) or a non-toxic, pharmaceutically acceptable salt or ester thereof to an implantation surgery patient.

9. The method according to claim 8 which comprises administering an amount, which is safe and sufficient to promote the formation of bone tissue, of a compound of

formula (I) or a non-toxic, pharmaceutically acceptable salt or ester thereof to a dental implantation surgery patient.

10. The method according to claim 9 wherein the compound administered is selected from the group consisting of clodronate, pamidronate, etidronate, alendronic acid, neridronic acid, risedronic acid, tiludronate, YM-175, BM-210995 and pharmaceutically acceptable salts and esters of said compounds.

11. The method according to claim 10 wherein the compound administered is clodronate or its pharmaceutically acceptable salt or ester.

12. The method according to claim 11 wherein the compound administered is clodronate disodium.

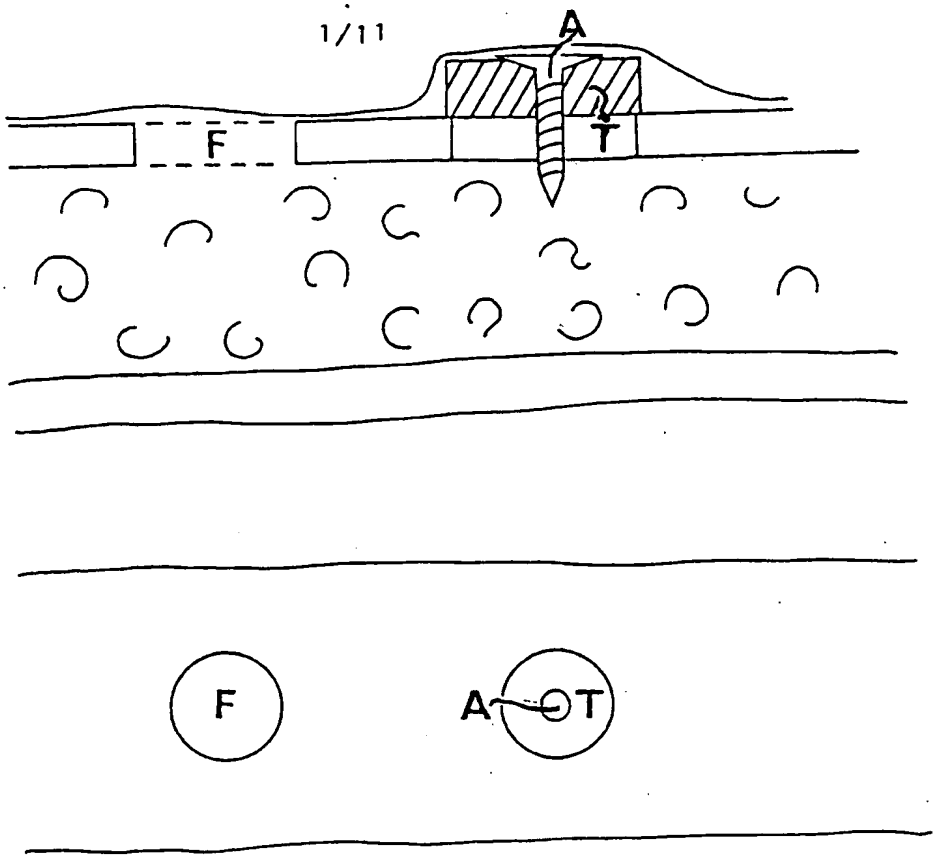


FIG. 1

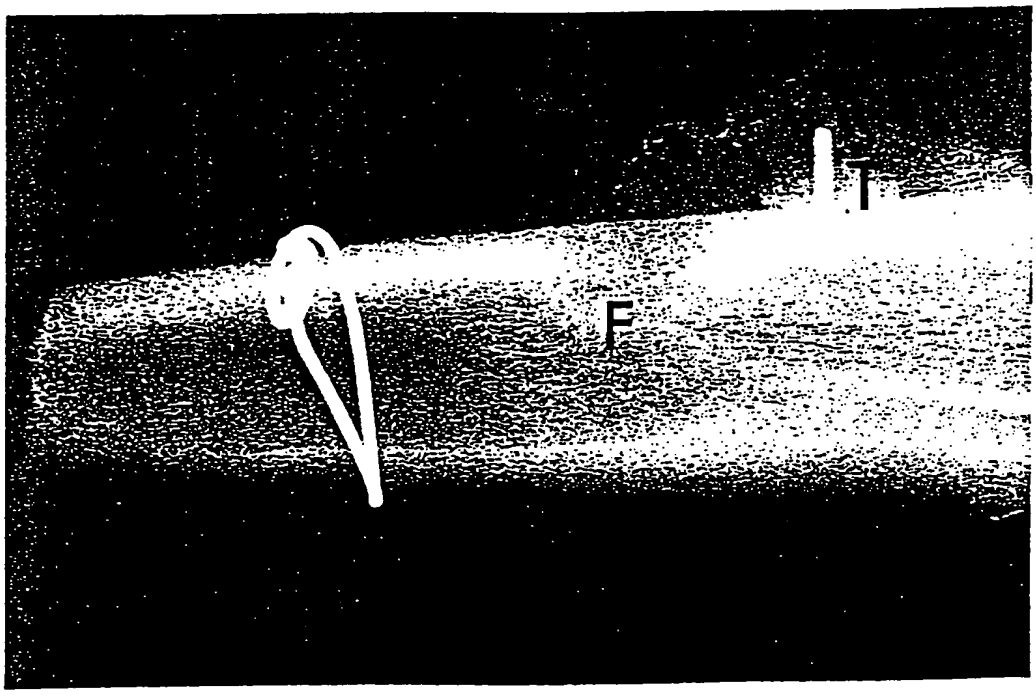


FIG. 2

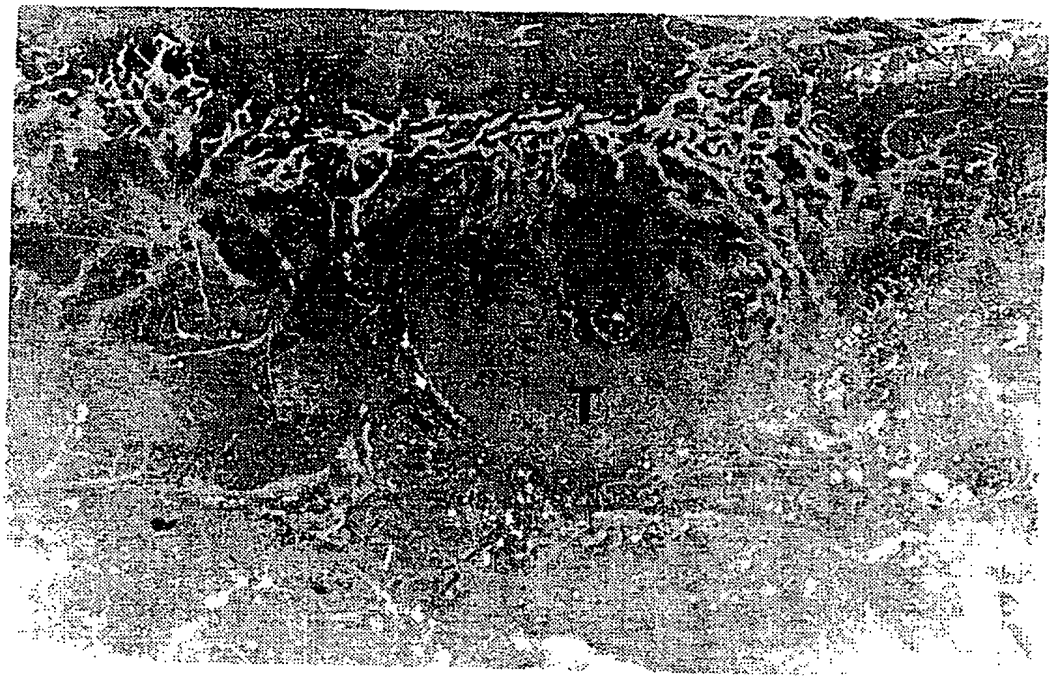


FIG. 3

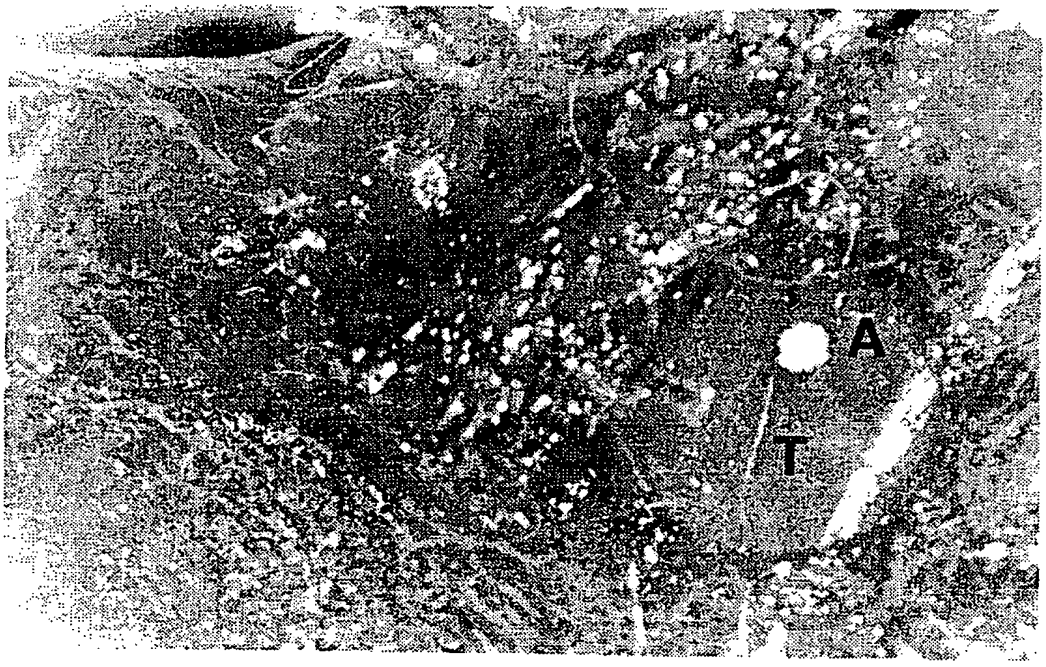


FIG. 4

FIG. 5

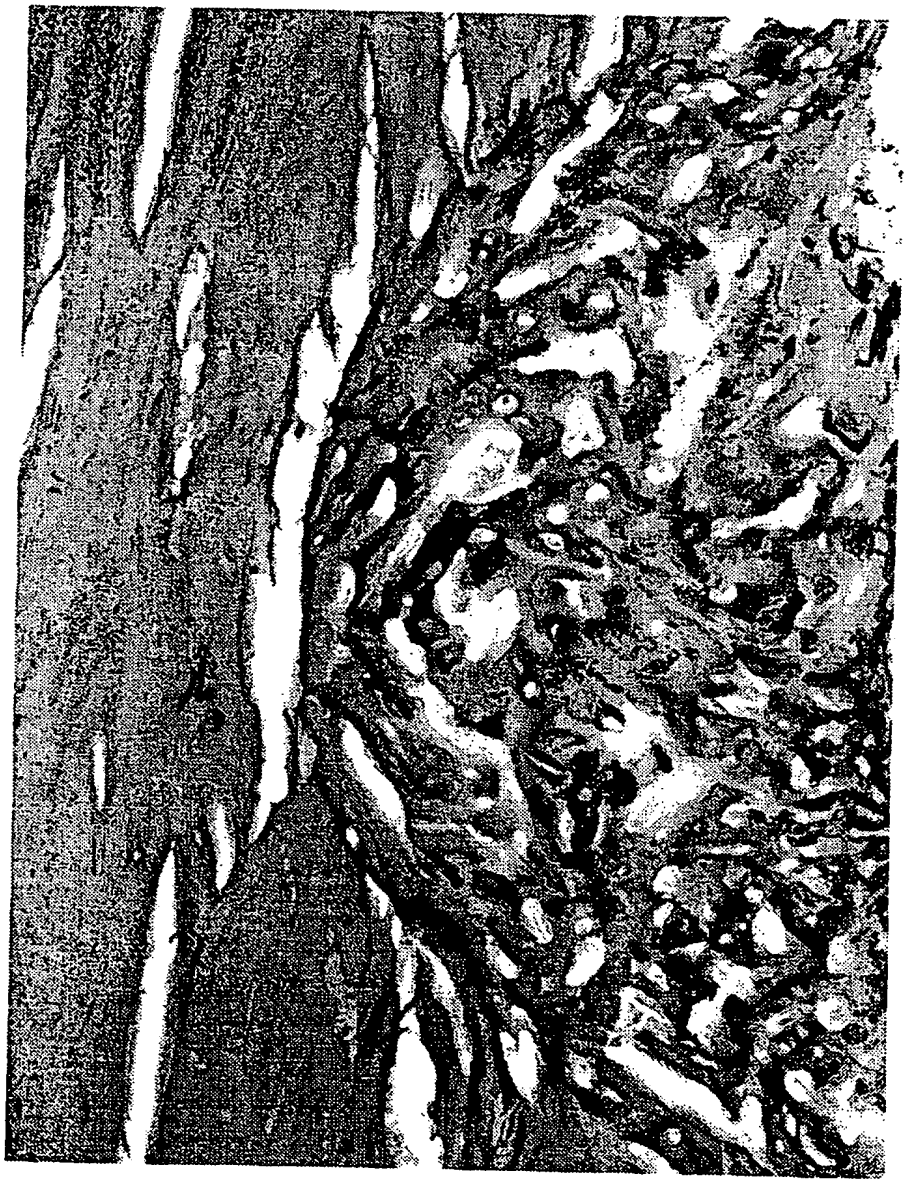


FIG. 6

FIG. 7

FIG. 8

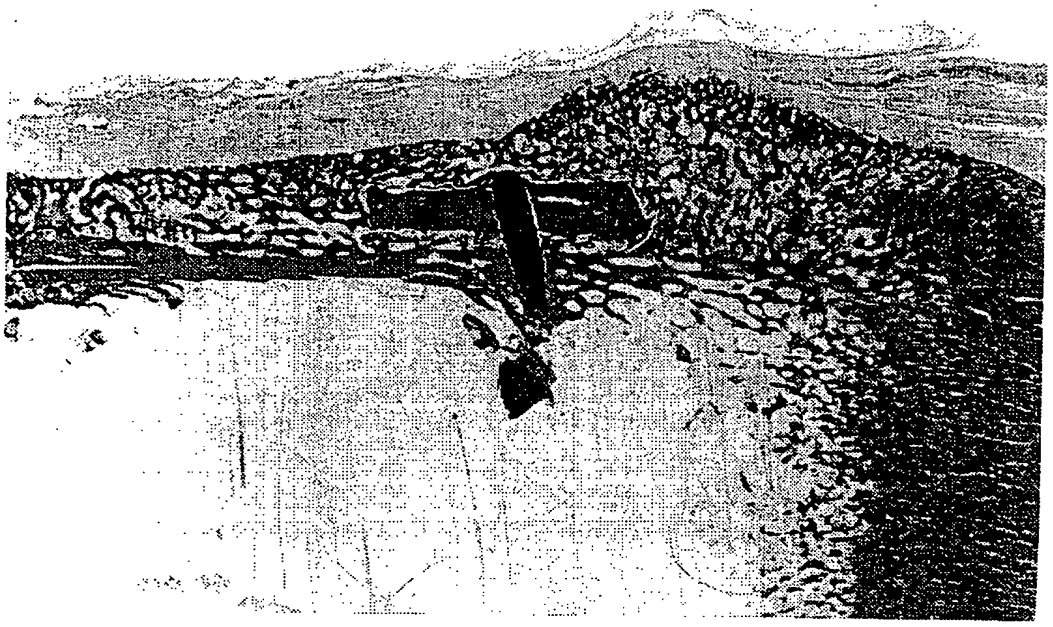


FIG. 9

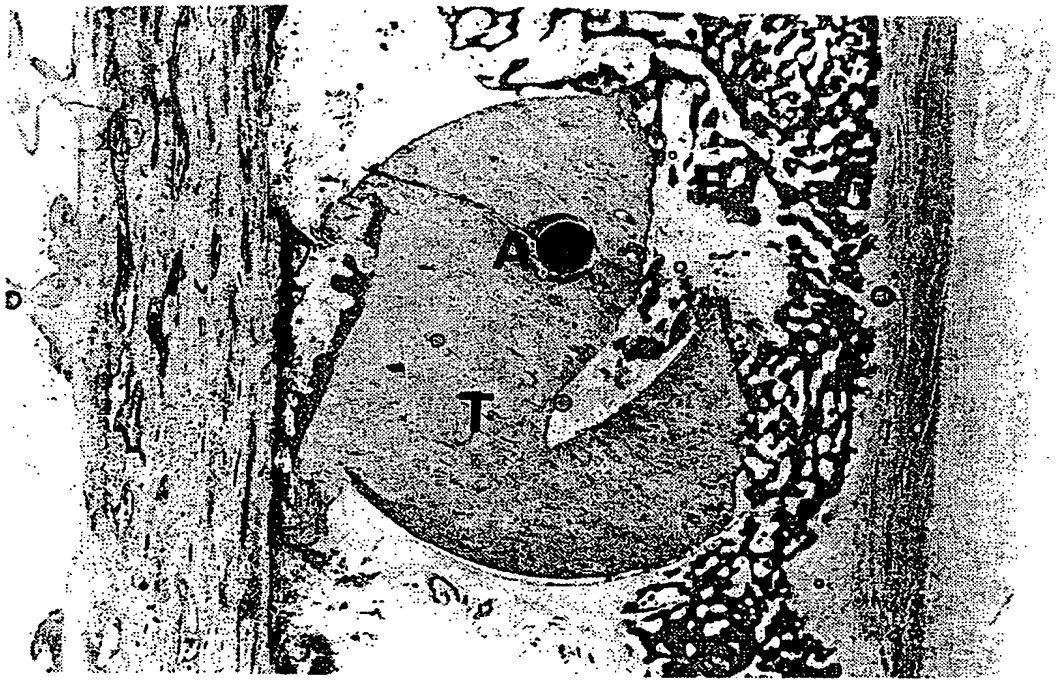


FIG. 10

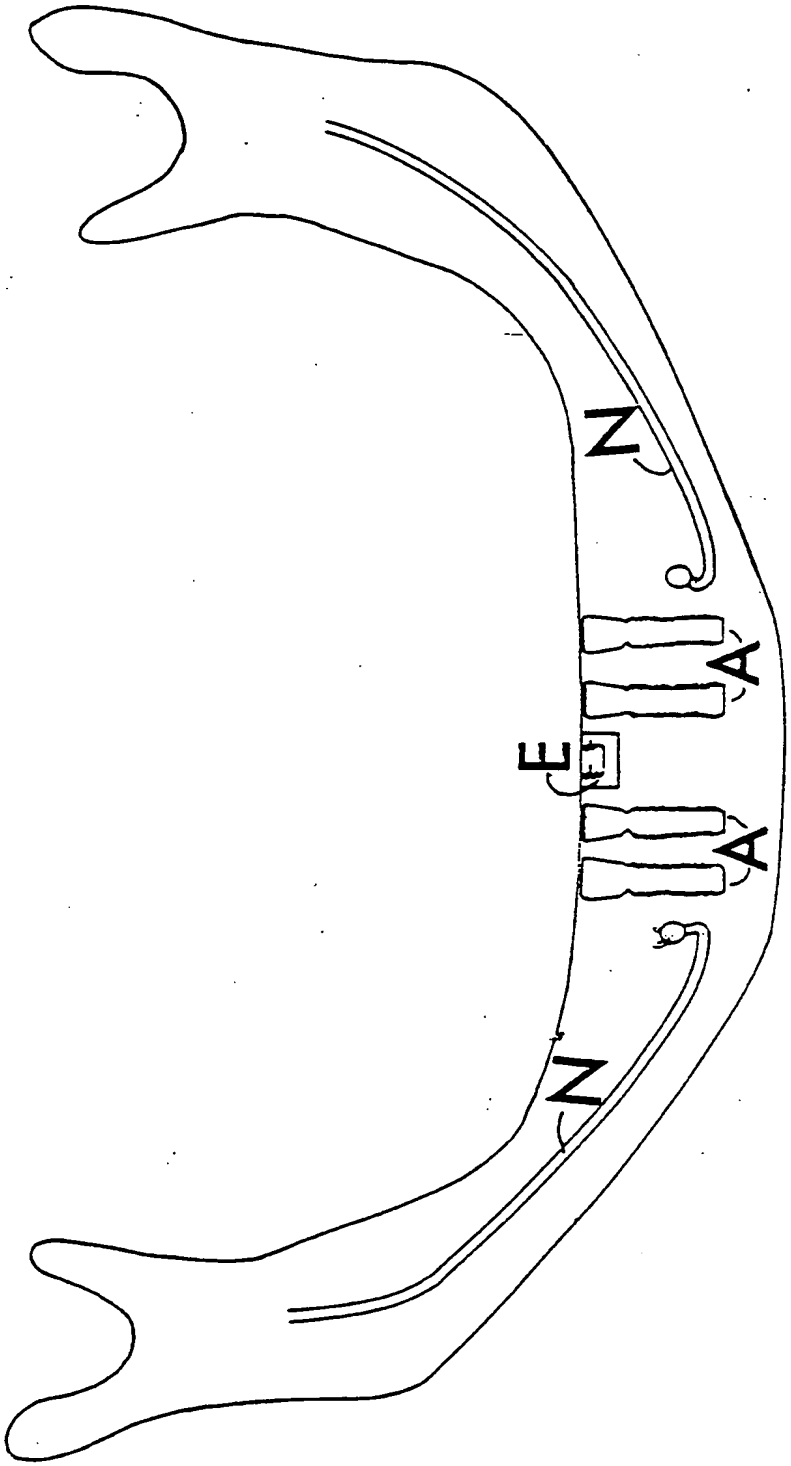


Fig.11

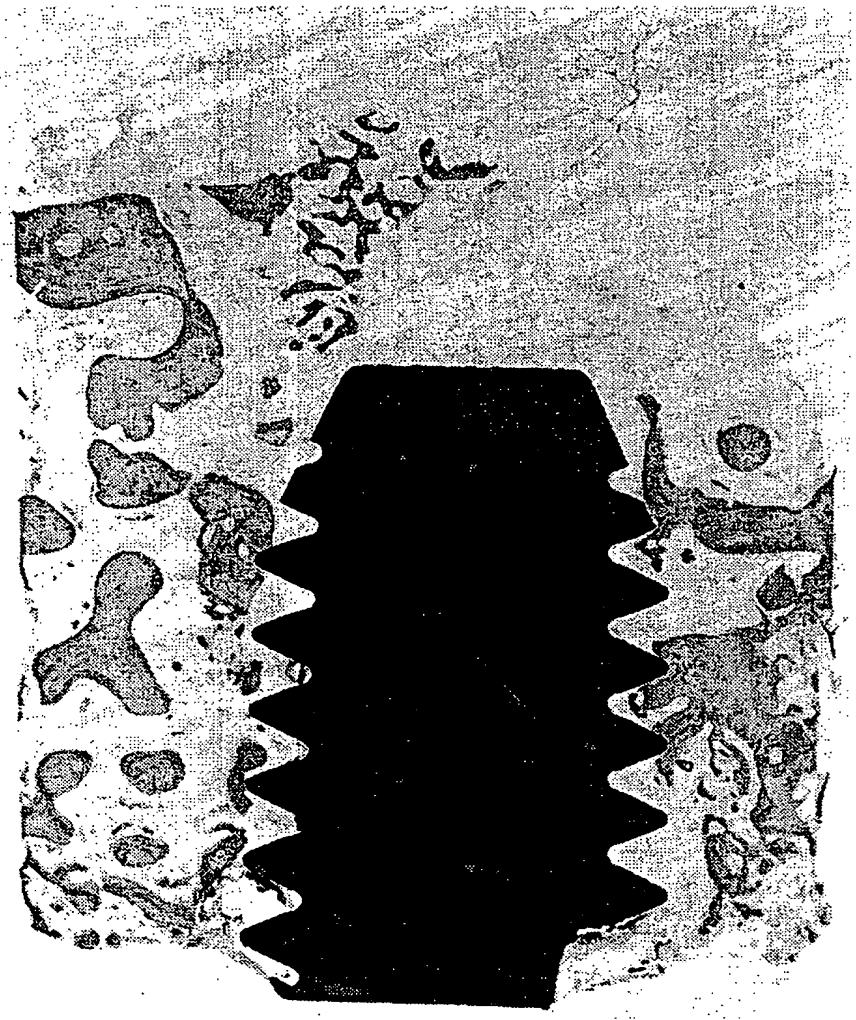


FIG. 12

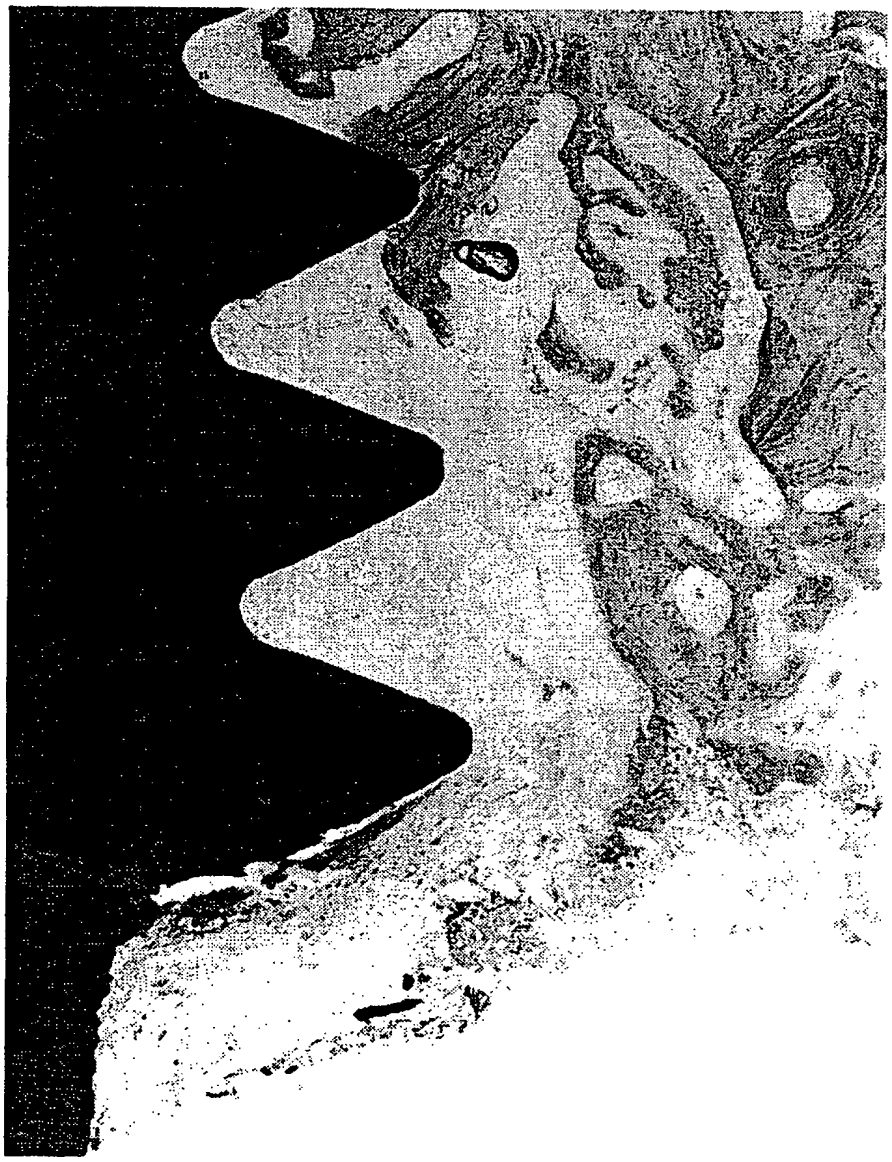


FIG. 13

FIG. 14

INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI 94/00091

A. CLASSIFICATION OF SUBJECT MATTER

IPC 5: A61K 31/66
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 5: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS-ONLINE, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PROG. CLIN. BIOL. RES., Volume 101, 1982, Julie glowacki, "Studies on the Regulation of Bone Synthesis and Bone Resorption", page 83 - page 91, see the whole document --	1-4
X	CLIN. ORTHOP. RELAT. RES., Volume 215, 1987, D.P. Rivero et al, "Effect of Disodium Etidronate (EHDP) on Bone Ingrowth in a Porous Material", page 279 - page 286, see the whole document --	1-2
X	US, A, 4753652 (ROBERT LANGER ET AL), 28 June 1988 (28.06.88), see the whole document --	1-4

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 June 1994	13 -07- 1994
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Göran Karlsson Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI 94/00091

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Chemical Abstracts, Volume 115, No 2, 15 July 1991 (15.07.91), (Columbus, Ohio, USA), page 455, THE ABSTRACT No 15663k, JP, A, 363062, (Hosonuma, Masashi et al) 19 March 1991 (19.03.91) -- --------	1-2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI 94/00091

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 5-12
because they relate to subject matter not required to be searched by this Authority, namely:

A method for treatment of the human or animal body by therapy, see Rule 39.1.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

28/05/94

International application No.
PCT/FI 94/00091

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A- 4753652	28/06/88	NONE	
JP-A- 363062	19/03/91	NONE	